Citation:

Ebbing M, Bleie O, Ueland PM, Nordrehaug JE, Nilsen DW, Vollset SE, Refsum H, Pedersen EK, Nygård O. Mortality and cardiovascular events in patients treated with homocysteine-lowering B vitamins after coronary angiography: A randomized controlled trial. *JAMA*. 2008; 300 (7): 795-804.

PubMed ID: 18714059

Study Design:

Randomized double-blind controlled trial

Class:

A - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To determine the effect of vitamin B_{12} plus folic acid supplementation on homocysteine levels, mortality and cardiovascular events among persons having undergone coronary angiography for suspected coronary artery disease (CAD) or aortic valve stenosis.

Inclusion Criteria:

- Persons participating in the Western Norway B Vitamin Intervention Trial (WENBIT)
- Male or female aged 18 years or older undergoing coronary artery angiography for suspected CAD or aortic valve stenosis at two University hospitals in western Norway.

Exclusion Criteria:

- Unavailable for follow-up
- Participating in other trials
- Had known alcohol abuse
- Had serious mental illness or cancer.

Description of Study Protocol:

Recruitment

- Patients at Haukeland University Hospital, Bergen, Norway (January 2000 to April 2004), and the recruitment period at Stavanger University Hospital, Stavanger, Norway (September 2000 to April 2004)
- A total of 5,630 patients underwent coronary angiography for stable angina pectoris, 4,216 for acute coronary syndromes and 395 for aortic valve stenosis.

Design

Randomized controlled trial.

Blinding Used

Double-blind.

Intervention

- Patients received a daily oral dose of one of the following treatments:
  - Folic acid, 0.8mg; vitamin B_{12} (cyanocobalamin), 0.4mg; and vitamin B_6 (pyridoxine), 40mg
  - Folic acid, 0.8mg; vitamin B_{12}, 0.4mg
  - Vitamin B_6, 40mg
  - Placebo
- Participants were asked to abstain from taking supplements containing B vitamins
- Adherence was judged by capsule counts and interviews. Participants were asked about hospital admissions and copies of hospital records were retrieved by mail. In addition, archives of the hospitals in western Norway were searched for information on all participants' hospital admissions and copies of records on possible events were collected. Data on deaths were obtained from the Cause of Death Registry and one incident cancer from the Cancer Registry in Norway, using the Norwegian unique 11-digit person number for each participant.

Statistical Analysis

- SPSS for Windows, version 15.0 (SPSS, Inc., Chicago, Illinois) and S-PLUS, version 7.0 (Insightful Corp, Seattle, Washington)
- Differences between intervention groups were determined by Chi-square tests for categorical variables and T-test or ANOVA for continuous variables
- The pre-specified analyses were comparison of treatment effect of folic acid plus vitamin B_{12} (groups one and two) with control (groups three and four) and comparison of treatment effect of vitamin B_6 (groups one and three) with control (groups two and four). Post-hoc overall comparison of treatment effect of the three different vitamin interventions with that of placebo
- Survival curves were constructed using the Kaplan-Meier method, and the differences in survival between groups were analyzed by the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (95% CI) were estimated using Cox proportional hazard regression with separate assessment for the folic acid plus vitamin B_{12} groups vs. control and the vitamin B_6 groups vs. control. All analyses were performed according to the intention-to-treat principle.

Data Collection Summary:

Timing of Measurements

Measurements were performed at baseline, one month, one year and at a final study visit. Planned median follow-up time was four years; however, the mean follow-up time was 38 months. If unable to attend visits, participants were interviewed over the phone.

Dependent Variables

- Variable 1 (primary endpoints):
  - Composite of all-cause death, nonfatal acute myocardial infarction (AMI), acute hospitalization for unstable angina pectoris and nonfatal thromboembolic stroke (infarction)
  - AMIs were classified according to the diagnostic criteria of the revised definition of MI published in 2000 and strokes according to definitions published in 2001
  - The following were included: Procedure-related nonfatal AMIs within 24 hours after coronary angiography, after PCI or after coronary artery bypass grafting (CABG)
  - Unstable angina pectoris: If patients were urgently admitted to the hospital, because of acute onset of typical ischemic symptoms accompanied by electrocardiographic ST-T findings of myocardial ischemia at rest and accompanied by coronary angiography during the same hospital stay verifying significant progression of CAD
- Variable 2 (secondary endpoints, determined from blood samples):
  - Glomerular filtration rates were estimated by the four-variable Modification of Diet in Renal Disease equations
  - Low-density lipoprotein cholesterol was calculated using the Friedewald formula. Blood samples for assessment of B vitamins and total homocysteine were stored at –80°C until analyzed in the laboratory of Bevital AS, Bergen, Norway.

Independent Variables

- Group 1: Folic acid, 0.8mg; vitamin B_{12}, 0.4mg; and vitamin B_6, 40mg
- Group 2: Folic acid, 0.8mg; vitamin B_{12}, 0.4mg
- Group 3: Vitamin B_6, 40mg
- Group 4: Placebo.

Control Variables

- Age
- Sex
- Smoking status
- Serum creatinine concentration.

Description of Actual Data Sample:

- *Initial N:* 3,090 patients were randomized (not all possible patients were screened because of capacity reasons)
- *Attrition (final N):* 2,121
- *Age:* 18 years and older
- *Other relevant demographics:* 20.5% female
- *Anthropometrics:* Baseline BMI was not different between groups
- *Location:* Western Norway.

Summary of Results:

- Mean follow-up was 38 months
- *Year one results:*
  - Mean serum folate concentration increased seven-fold and mean serum cobalamin concentration increased by 65% in the groups receiving folic acid plus vitamin B_{12}
  - Mean plasma pyridoxal phosphate concentration increased nine-fold in the groups receiving vitamin B_6
  - Mean plasma total homocysteine level was decreased by 30%, from 10.8µmol per L (SD, 4.5) at baseline to 7.6µmol per L (SD, 2.2) in the groups receiving folic acid and vitamin B_{12} ($P<0.001$)
  - Plasma total homocysteine concentration remained unaltered in the groups receiving vitamin B_6 alone or placebo.
- *Final study visit:*
  - Mean plasma total homocysteine level was 2.8µmol per L lower in the folic acid plus B_{12} groups than in the non-folic acid groups (a difference of 26%; $P<0.001$)
  - 422 participants (13.7% of all) experienced an event in the composite primary end point of death, AMI, unstable angina pectoris or thromboembolic stroke. A total of 219 participants (14.2%) in the groups receiving folic acid vs. 203 participants (13.1%) in the groups not receiving folic acid experienced the primary endpoint (HR, 1.09; 95% CI, 0.90 to 1.32; P=0.36). In the groups receiving vitamin B_6, 200 participants (13.0%) experienced the primary end point compared with 222 (14.3%) in the groups not receiving vitamin B_6 (HR, 0.90; 95% CI, 0.74 to 1.09; P=0.28)
  - 157 participants (12.2%) in the groups receiving folic acid groups vs. 146 (11.8%) of those not receiving folic acid experienced the primary endpoint (HR, 1.04; 95% CI, 0.83 to 1.30; P=0.75). In the groups receiving vitamin B_6, 139 participants (11.0%) who adhered to study medication experienced the primary endpoint vs. 164 (12.9%) of those not receiving vitamin B_6 (HR, 0.85; 95% CI, 0.68 to 1.06; P=0.15)
  - There were no differences in treatment response for the separate endpoints of death, total AMI (fatal and non-fatal, including procedure-related) or unstable angina pectoris
  - The incidence of total stroke (fatal and non-fatal, including hemorrhagic) was not significantly lower in the groups receiving folic acid. The incidence of acute hospitalization due to angina pectoris was lower in the folic acid groups (HR, 0.82; 95% CI, 0.67 to 1.00; P=0.05)
  - Post-hoc overall survival analysis: no differences between the groups (P=0.07)
- Increased risk of the composite primary endpoint in the group receiving folic acid plus vitamin B_{12} (HR, 1.34; 95% CI, 1.03 to 1.75; P=0.03) compared with placebo
- The baseline level of total homocysteine in plasma was a significant predictor of the primary endpoint (HR associated with a 3µmol per L difference in total homocysteine level, 1.07; 95% CI, 1.02 to 1.13; P=0.01) after adjustment for age, sex, smoking status (never, ex-, or current smoker) and serum creatinine concentration.

Author Conclusion:

There was no preventive effect of intervention with folic acid plus vitamin B_{12} or with vitamin B_6 on mortality or major cardiovascular events among patients with mainly stable CAD undergoing intensive conventional treatment, despite a numerically lower incidence of stroke and higher incidence of cancer in the groups receiving folic acid.

Reviewer Comments:

The following limitations were noted by the authors:

- *Inability to consecutively screen all possible eligible participants made the inclusion process non-transparent. However, they state that this did not bias randomization*
- *The power of the trial was less than planned.*

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions		
1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	Yes
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	Yes

Validity Questions		
1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes

2.4.	Were the subjects/patients a representative sample of the relevant population?	???
3.	**Were study groups comparable?**	Yes
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	Yes
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	Yes
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	Yes
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	N/A
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	???
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	Yes
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	N/A

5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	Yes
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	N/A
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	???
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	Yes
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	Yes
6.6.	Were extra or unplanned treatments described?	Yes
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	Yes
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	N/A
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	???
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	???
7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes

8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	Yes
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
8.6.	Was clinical significance as well as statistical significance reported?	Yes
8.7.	If negative findings, was a power calculation reported to address type 2 error?	Yes
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**	Yes
9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**	Yes
10.1.	Were sources of funding and investigators' affiliations described?	Yes
10.2.	Was the study free from apparent conflict of interest?	Yes